Abstracts

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Genetically Elevated C-Reactive Protein and Ischemic Vascular Disease

Zacho J, Tybjaerg-Hansen A, Jensen JS, et al. N Engl J Med 2008;359: 1897-908.

Conclusion: Polymorphisms of the C-reactive protein (CRP) gene are associated with increases in CRP levels but are not in themselves associated with an increased risk of ischemic vascular disease.

Summary: It is well known that elevated plasma levels of CRP are associated with an increased risk of ischemic cerebrovascular and ischemic cardiac disease. What is unknown is whether CRP levels themselves contribute to causation of ischemic cerebrovascular or cardiac disease, or are merely markers of the existence of ischemic cerebrovascular or cardiovascular disease. The CRP gene has genetic variations that increase levels of CRP to different degrees and therefore can theoretically be used to assess the consequences of lifelong high CRP levels independent of additional risk factors. The authors of this study sought to determine whether genetically elevated CRP levels caused an increased risk of ischemic heart disease and ischemic cerebrovascular disease.

The study included 10,276 people from a general population cohort. Ischemic heart disease developed in 1786, and ischemic cerebrovascular disease developed in 741. In an additional cohort of 31,992 persons from the general population, 2521 had ischemic heart disease and 1483 had ischemic cerebrovascular disease. The authors also studied an additional 2238 patients with ischemic heart disease and 4474 control participants along with 612 patients with ischemic cerebrovascular disease and an additional 1224 control participants. High-sensitivity CRP was measured, followed with genotyping of four CRP polymorphisms and two apolipoprotein E polymorphisms.

In persons with CRP levels >3 mg/L, compared with those with CRP levels <1 mg/L, ischemic heart disease was increased by a factor of 1.6 and ischemic cerebrovascular disease was increased by a factor of 1.3. The four CRP polymorphisms resulted in an increase in CRP levels of up to 64%. Theoretically, this would predict an increased risk of 32% for ischemic heart disease and 25% for ischemic cerebrovascular disease. However, no genotype combination was associated with an increased risk of either ischemic cerebrovascular or ischemic cardiac disease. Apolipoprotein E genotypes were associated with an increased risk of ischemic heart disease and elevated cholesterol levels.

Comment: Drugs are being developed to specifically target lowering CRP levels (Curr Atheroscler Rep 2006;8:421-8). The ultimate goal would be to lower CRP levels and, if CRP is associated with causing atherosclerosis, ultimately prevent the development of vascular disease. This study suggests that such a strategy is likely to be "barking up the wrong tree." Although epidemiologic studies have observed an increased risk of ischemic vascular disease associated with higher plasma CRP levels, the current data indicate that increased CRP levels are perhaps more a marker for atherosclerosis than a cause of atherosclerosis. Please see also the abstract for a related article (N Engl J Med 2008;359:2195-207).

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Ridker, PM, Danielson E, Fonseca FAH, and the JUPITER Study Group. N Engl J Med 2008;359:2195-207.

Conclusions: In patients with elevated high-sensitivity C-reactive protein (CRP) levels, who are otherwise apparently healthy without hyperlipidemia, rosuvastatin significantly reduced major cardiovascular events.

Summary: Increased levels of CRP, an inflammatory biomarker, predict cardiovascular events. Statin medications have been known to lower cholesterol and levels of high-sensitivity CRP. The authors hypothesized that patients with elevated high-sensitivity CRP levels, but with normal lipid levels, might benefit from statin treatment. This was a randomized prospective clinical trial comprising 17,802 apparently healthy women and men with low-density lipoprotein cholesterol (LDL-C) levels <130 mg/dL and with high-sensitivity CRP levels ≥2.0 mg/dL. Patients were randomly assigned to rosuvastatin (20 mg daily) or placebo. They were then monitored for the occurrence of the primary end point of myocardial infarction, arterial revascularization, hospitalization for unstable angina, stroke, or death from cardiovascular causes.

After a median of 1.9 years of follow-up, the trial was stopped by the safety monitoring committee. LDL-C levels were reduced by rosuvastatin by 50% and high-sensitivity C-reactive protein levels were reduced by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 patient-years of follow-up in the rosuvastatin and placebo groups, respectively. Rosuvastatin had a hazard ratio (HR) of 0.56 (95% confidence interval [CI], 0.46-0.69; $P < .00001$). Rates for myocardial infarction were 0.17 and 0.37 per 100 person-years in the rosuvastatin and placebo groups, respectively (HR, 0.46; 95% CI 0.30-0.70; $P = .0002$). For stroke, corresponding rates for 100 person-years were 0.18 and 0.34 for rosuvastatin and placebo groups (HR, 0.52; 95% CI 0.34-0.79; $P = .002$). Rates per 100 patient-years for revascularization or unstable angina were 0.41 and 0.77 for the rosuvastatin and placebo groups, respectively (HR, 0.53; 95% CI, 0.40-0.7; $P < .00001$). For a combined end point of myocardial infarction, stroke, or death from cardiovascular causes, the rates for rosuvastatin and placebo per 100 patient-years were 0.45 and 0.85, respectively (HR, 0.53; 95% CI 0.4-0.69; $P < .00001$). Finally, for death from any cause, rates for rosuvastatin and placebo were 1.00 and 1.25 per 100 patient-years, respectively (HR, 0.80; 95% CI, 0.67-0.97; $P = .02$). No significant increase in myopathy or cancer was noted in the rosuvastatin patients, but they did have a higher incidence of diabetes.

Comment: The findings of this study are compatible with the now well-accepted postulate that inflammation contributes to and is essential to the atherosclerotic process. This study was stopped relatively soon after its inception, and this raises the possibility that the events that occurred may be independent of the usual mechanisms of progression of atherosclerotic plaque. It does seem unusual that patients who have LDL-C levels that are generally regarded as favorable would have marked progression of atherosclerosis in such a short time. The results may therefore indicate more of a plaque stabilization effect of lowering CRP levels than inhibition of bulky progression of existing plaque. The article should be examined in the context of another article, also from the *New England Journal of Medicine* (N Engl J Med 2008;359:1897-908), that is also abstracted in this issue of the *Journal of Vascular Surgery*. This second article suggests that treatment of CRP alone would be unlikely to be of benefit in patients at risk for cardiovascular events. However, the two articles are not necessarily incompatible. It is reasonable to postulate that to derive benefit from treatment of elevated CRP, it is also necessary to drive down the LDL-C level. Trials will eventually be required with agents that can lower CRP—but not affect cholesterol levels—to tease out the mechanism of benefit of rosuvastatin therapy in patients with otherwise "acceptable" LDL-C levels and elevated CRP.

Anatomic Suitability of Ruptured Abdominal Aortic Aneurysms for Endovascular Repair

Slater BJ, Harris EJ, Lee JT. Ann Vasc Surg 2008;22:716-22.

Conclusions: Only about half of patients with ruptured abdominal aortic aneurysms (rAAAs) are candidates for endovascular aneurysm repair (EVAR) with conventional stent graft devices.

Summary: Open surgical repair is the traditional strategy to treat patients with rAAAs. The mortality rate is approximately 50%. There is now considerable enthusiasm for EVAR of rAAAs. Small case series suggest EVAR is feasible for rAAAs and may be associated with improved short-term morbidity and mortality compared with open repair. Only one randomized controlled study has compared open vs endovascular repair of rAAAs, however, and it showed no difference in outcome (Eur J Vasc Endovasc Surg 2006;32:506-14).

The authors sought to investigate anatomic suitability of rAAAs for EVAR by review of preoperative cross-sectional imaging. They retrospectively analyzed a consecutive series of rAAAs. Imaging studies were used to determine if EVAR could have been feasible based on available devices at the time of data collection for the study. If the patients had an aortic neck diameter >32 mm, a neck length <10 mm, neck angulation >60° severe iliac tortuosity, or external iliac artery diameters <6 mm, they were declared noncandidates for EVAR.

During a 10-year period, 47 rAAAs were treated at this institution, of which 60% were transferred from referring hospitals and 47% had free rupture. During the past 2 years, five (11%) had been treated with EVAR, and the remaining 42 patients underwent open repair. Preoperative imaging was available in 43 of the 47 patients treated. Morphologic measurements based on the criteria noted above indicated 49% would have been candidates for EVAR. EVAR was precluded by inadequate neck length in 73%, unsuitable iliac access in 23%, large neck diameter in 18%, and severe angulation of the aneurysm neck in 14%. The 30-day operative mortality rate was 34%, and 1-year mortality was 42%. EVAR candidates were more likely to be men (95% vs 68%, $P = .046$), to have smaller sac diameters (7.0 vs 8.5 cm, $P = .0.2$), and longer length necks (24.1 vs 8.6 mm, $P < .0001$). They were also less likely to have >60° angulated neck (10% vs 45%, $P = .0002$) and more likely to have larger external iliac artery diameters (8.9 vs 7.3 mm, $P = .015$).

Comment: The results of this study, using a retrospective analysis of cases up to 10 years ago, would seem to be relatively applicable to the anatomy of patients currently with rAAAs. Anatomy of rAAAs is unlikely to